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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SPIEGLER, ALEXANDER H	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,751	PARRINGTON ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Sequence Notes

1. The Sequence Listing filed in this application complies with the requirements of 37 CFR 1.821-1.825 and has been entered.

Information Disclosure Statement

2. The information disclosure statement of Paper No. 8 complies with CFR 1.97, 1.98, and M.P.E.P. 609, and has been considered.

Specification

3. The disclosure is objected to because of the following informalities:

A) The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

B) The drawings contain Figures 1A, 1B, 2A, 2B, 5A, 5B and 5C, however the specification does not provide a detailed description for each Figure. On page 6, the specification generally describes Figures 1-6, but does not describe the Figures listed above, 1**A**, 1**B**, etc. Applicants should amend the specification to describe every Figure. It is also noted, there is a Figure 3A, but no 3B. Applicants could amend the drawings to only recite "Figure 3".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-14 over "internal transcribed sequence" because it is not clear as to exactly what an "internal transcribed sequence" encompasses.

MPEP 2173.02 discusses 35 U.S.C. 112, 2nd paragraph:

The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;
(B) The teachings of the prior art; and
(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g., *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000)... If the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty, a rejection of the claims under 35 U.S.C. 112, second paragraph is appropriate. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973).

In the instant case, the recitation of "internal transcribed sequence" is not defined in the specification. Additionally, "internal transcribed sequence" is found in only one US patent (USPN 6,071,737), but this patent does not define what is specifically meant by an "internal transcribed sequence". Accordingly, the prior art, the specification and the claims fail to set out and circumscribe "internal transcribed sequence" with a reasonable degree of clarity and particularity.

B) Claims 1-14 over "corresponding to" because this is not an art recognized term to describe the relationship between two nucleic acid sequences. It is not clear whether this refers to sequence homology/similarity or to sequence complementarity, and furthermore, it is not clear as to what percentage of homology or complementarity is encompassed by "corresponding" or under what types of conditions "corresponding" nucleotides/sequences are determined. Specifically, it is unclear as to how a labeled sequence "corresponds" to an internal transcribed sequence or how a primer "corresponds" to transcribed sequences, absent clear guidance in the specification.

C) Claims 1-14 because the claims state, "amplified transcribed target RNA" (see claims 1 and 4) and "the PCR product" (see claim 12), however, claims 1 and 12 do not comprise and actual step of obtaining an "amplified transcribed target RNA" or "PCR product". Applicants could amend the claims to recite a specific "obtaining" step.

D) Claims 3-7 and 9 over "effected" because it is not clear as to how regression analysis "effects" the comparison between the bound labeled sequence and the RNA standard. It is suggested that Applicants amend the claims to clearly state the comparison is carried using regression analysis. Claim 6 is furthered indefinite over "said binding step is effected by effecting", which is generally vague and confusing in the English language.

E) Claims 5 over "said label" because this recitation lacks antecedent basis.

F) Claim 8 is indefinite because it is not clear if "a single enzyme reaction" means the RT and the PCR reaction occur in one tube with one enzyme, or the RT reaction uses a single enzyme, and the PCR uses a single enzyme.

G) Claim 12 over "(PCR)" because it is not clear as to whether this claim specifically requires PCR (also known as polymerase chain reaction) or some other DNA polymerase amplification reaction.

H) Claims 13-14 over "more accurately" because it is not clear as to what this method is being compared to for one to conclude the method quantifies "more accurately" than another method.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-4, 6-8 and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Gibson et al. (Genome Research (1996) 6: 995-1001, cited in the IDS).

Gibson teaches a methods for real time quantitative RT-PCR. Specifically, Gibson teaches:

a) isolating RNA from a tissue sample (pgs. 999-1000, for example);

b) subjecting the isolated RNA to RT-PCR (pgs. 997 and 1000-01, for example);

c) binding a labeled sequence (e.g., fluorescently labeled) corresponding to an internal transcribed sequence of the target RNA to amplified transcribed target RNA (pgs. 997-99 and 1001, for example);

d) determining the amount of labeled sequence bound to amplified transcribed target RNA ((pgs. 997-99 and 1001, for example);

e) establishing an RNA standard of the number of copies of the target RNA (pgs. 997-98, for example);

f) comparing the determined amount of bound labeled sequence in the sample to the RNA standard as a measure of the number of copies of target RNA in the tissue sample (pgs. 997-99, see also Figs. 1-3, for example).

Gibson also teaches synthesizing, quantifying and serial diluting a synthetic RNA standard (pgs. 997-99, for example). Gibson teaches the RNA standard is amplified via RT-PCR, then binding a labeled probe to the amplified transcribed synthetic RNA molecule (pgs. 1000-01, for example). Gibson also teaches determining the quantity of labeled sequence bound, and plotting the individual determination against a known starting copy number (pgs. 996-998 1000-01, and Figs. 1-3, for example).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gibson et al. (Genome Research (1996) 6: 995-1001, cited in the IDS), as applied to claims 1-4, 6-8 and 11-14 above, and further in view of Martin et al. (Biotechniques (1995) 18(5) 908-913).

The teachings of Gibson are presented above. Specifically, Gibson teaches RT-PCR, wherein the PCR products are detected via a fluorescently labeled probe. Gibson does not teach using a radioactively labeled probe.

However, Martin teaches the use of radioactively labeled probes for detection of PCR products (pgs. 908-910). Specifically, Martin teaches the detection of PCR products via radioactively labeled probes leads to a sensitive quantitation of the target (pg. 909).

In view of the teachings of Martin, it would have been obvious to one of ordinary skill in the art at the time the invention to have used radioactively labeled probes to detect the PCR products of an RT-PCR reaction, as an alternative and equally effective means of detection, in order to have achieved the benefit of providing a sensitive quantitation of the target sample.

10. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gibson et al. (Genome Research (1996) 6: 995-1001, cited in the IDS), as applied to claims 1-4, 6-8 and 11-14 above, and further in view of Mulder et al. (J. Clin. Microbiol. (1994) 32 : 292-300).

The teachings of Gibson et al. are presented above. Specifically, Gibson teaches a quantitative RT-PCR method using AMV and *Tfl* polymerase, Taqman probes and an internal RNA standard. Gibson does not teach using *Thermus thermophilus* (also referred to as r*Tth* DNA polymerase).

However, Mulder teaches using *Thermus thermophilus* is advantageous when used in carrying out RT-PCR.

Specifically, Mulder teaches:

> [W]hereas conventional reverse-transcriptase-PCR assays involve a two-step process and use two enzymes, the method described uses a single enzyme, r*Tth* DNA polymerase, for both reverse transcription and PCR. The reactions are carried out in a single tube and with a single buffer solution with uninterrupted thermal cycling.

(see abstract).

Accordingly, Mulder teaches the use of only one enzyme is needed when using *Thermus thermophilus* in RT-PCR, thus providing a more efficient and less contaminant-prone reaction (see also pg. 292-293 and 297-299).

In view of the teachings of Mulder, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gibson so as to have used only a single enzyme, e.g., Thermus thermophilus, instead of using both AMV and *Tfl* polymerase, in order to have achieved the benefit of providing an a more efficient and effective means of quantification.

11. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gibson et al. (Genome Research (1996) 6: 995-1001, cited in the IDS), as applied to claims 1-4, 6-8 and 11-14 above, and further in view of Sullivan (USPN 5,958,912).

The teachings of Gibson et al. are presented above. Specifically, Gibson teaches an advantageous method of quantitative RT-PCR method using a fluorescent probe. Gibson also teaches this method is a general method which is applicable to other targets (pgs. 995-996 and 998-999), but does not teach the use of a cytokine as a target.

However, Sullivan teaches the detection of cytokines (e.g., TGF-B, IL-1, IL-6, etc.) via RT-PCR is beneficial in detecting Sjogren's syndrome (cols. 11-16).

In view of the teachings of Sullivan, it would have been obvious to one of ordinary skill in the art at the time the invention to have detected a cytokine using the quantitative RT-PCR methods of Gibson, in order to have detected Sjogren's syndrome for use in treatment and evaluation of therapy.

Conclusion

12. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Ken Horlick, can be reached at (703) 308-3905. If attempts to reach Ken Horlick are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
June 16, 2003

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
6/17/03